Psychiatry Research 280 (2019) 112519

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Case report

Blast exposure interacts with genetic variant 5HTTLPR to predict posttraumatic stress symptoms in military explosives personnel

Marcus K. Taylor[a], Lisa M. Hernández[a,b,*], Jeremy Stump[a,b], Anna E. Tschiffely[c], Carl W. Goforth[c], D. Christine Laver[a,b], Stephen T. Ahlers[c]

[a] Biobehavioral Sciences Lab, Warfighter Performance Department, Naval Health Research Center, San Diego, CA, USA
[b] Leidos, Inc., San Diego, CA, USA
[c] Neurotrauma Department, Operational and Undersea Medicine Directorate, Naval Medical Research Center, Silver Spring, MD, USA

ARTICLE INFO

Keywords:
Blast exposure
Genetics
Posttraumatic stress

ABSTRACT

The first of its kind, this study determined whether blast exposure interacts with genetic variant 5HTTLPR to predict posttraumatic stress (PTS) symptoms in 78 military explosives operators. In all models, blast-exposed 5HTTLPR S carriers registered definitively higher PTS symptoms in comparison to non-exposed S carriers, as well as exposed and non-exposed LL carriers (all $p < 0.01$). All findings were robust to confounding influences of age and traumatic brain injury diagnosis. Not only is blast exposure prevalent in EOD personnel, but it also interacts with genetic predisposition to predict trauma symptoms in this unique, at-risk military population.

1. Introduction

Posttraumatic stress disorder (PTSD) is a leading military health concern (Walter et al., 2018; Armenta et al., 2018; Xue et al., 2015). One critical risk factor is blast exposure, which is widely recognized as the "signature injury" of the military conflicts in Iraq and Afghanistan (DePalma and Hoffman, 2018). The entanglement of blast exposure and posttraumatic stress (PTS) symptoms is exceedingly complex (Tschiffely et al., 2015), constituting one of the foremost "wicked problems" (Churchman, 1967) facing the military community in the 21st century.

While some individuals clinically improve after blast exposure, others do not (Cole and Bailie, 2016). With this in mind, genetic predisposition is a plausible moderator of the link between blast exposure and PTS (Elder et al., 2012), but this topic persists as a profound knowledge gap. A plausible genetic variant – 5HTTLPR – combines reliably with stressful life events to amplify PTS (Zhao et al., 2017), depression, and suicidality (Caspi et al., 2010). However, published reports linking 5HTTLPR to behavioral health outcomes in military members are few (Wald et al., 2013) and it remains unclear whether blast exposure and 5HTTLPR combine to predict PTS. In this study, we sought to determine if blast exposure interacts with 5HTTLPR to predict PTS in U.S. Navy EOD personnel.

2. Methods

As part of the EOD Operational Health Surveillance System, 78 military men from EOD Group ONE (San Diego, CA, USA) were studied ($M \pm SE$age = 34.1 ± 0.7 years). This investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study design was reviewed by an appropriate ethical committee, the Naval Health Research Center Institutional Review Board, and approved under the research protocol NHRC.2015.0013. Informed consent of the participants was obtained after the nature of all study procedures had been fully explained.

2.1. Blast exposure

Blast exposure was estimated with two separate self-report items, inspired by two events identified within the Deputy Secretary of Defense (2010) Directive-Type Memorandum 09–033, as requiring mandatory command evaluations and reporting of exposure. Participants first indicated whether they had been within 50 m of a blast within their military career (yes/no). Next, they reported whether they had been involved in a vehicle crash or blast during their military career (yes/no). Preliminary face, convergent, and divergent validity has been established for both items in our unpublished studies.

* Corresponding author at: Biobehavioral Sciences Lab, Warfighter Performance Department, Naval Health Research Center, 140 Sylvester Road, San Diego, CA, 92106, USA.
E-mail address: lisa.m.hernandez75.ctr@mail.mil (L.M. Hernández).

https://doi.org/10.1016/j.psychres.2019.112519
Received 17 June 2019; Received in revised form 1 August 2019; Accepted 14 August 2019
Available online 14 August 2019
0165-1781/

2.2. Determination of genotypes

We evaluated 5HTTLPR following our previously-described protocol (Taylor et al., 2017).

2.3. PTS symptoms

The PTSD Checklist for *DSM-5* (PCL-5) was used to assess PTS symptoms (Weathers et al., 2013). Cronbach's alpha coefficient for this scale in the present study was 0.93.

2.4. Data reduction and analysis

Data were analyzed using IBM SPSS Statistics, version 23.0 (Armonk, NY, USA). Descriptive analyses were conducted to summarize subject characteristics. Distribution characteristics for continuous variables (e.g., PTS symptoms) were examined following standard criteria (Leech et al., 2005; Taylor et al., 2016). Variables exceeding normality limits were transformed prior to performing the relevant statistical test. All data transformations reduced skewness and kurtosis to acceptable levels. Untransformed means are reported for ease of interpretation. Tests for departure from Hardy–Weinberg equilibrium were performed via χ^2 test for goodness of fit (Lewis and Knight, 2012). Genotypes were decomposed into alleles according to a "dominant S" model (i.e., SL + SS vs. LL) (Lewis and Knight, 2012). Unique associations of blast exposure and genetic predisposition (respectively) with PTS symptoms were first explored with ANOVA. Participants were then categorized into four groups based on presence versus absence of the S allele and blast exposure (i.e., S/blast; S/no blast; LL/blast; LL/no blast). This was performed iteratively for each of the two blast exposure items and for each of the two 5HTTLPR versions. Thus, four combined models were tested. Overall models were evaluated with one-way ANOVA and Bonferroni-corrected post-hoc group comparisons ($\alpha = 0.05/3 = 0.017$). Effect sizes were estimated via partial eta squared (η^2_p; Richardson, 2011), and observed power ($1-\beta$) was computed. Potential interaction effects were appraised by post-hoc group comparisons, as well as interpretation of group/marginal means. Theoretically relevant variables (i.e., age and TBI diagnosis) were evaluated as potential covariates following predefined criteria (MacKinnon et al., 2000; Taylor et al., 2017). All hypothesis tests were two-sided, and the probability of committing a type I error was set at 0.05.

3. Results

Nearly two-thirds of participants reported being within 50 m of a blast, and one-third of participants reported involvement in a vehicle crash or blast during their military career. Most participants (82%) endorsed PTS symptoms, yet very few met criteria for probable PTSD (PCL-5 score $\geq$ 38; $n = 3$ [3.8%]). This sample did not depart from Hardy–Weinberg equilibrium with respect to the biallelic ($\chi^2(2, N = 76) = 0.72$, $p = 0.70$) or triallelic version ($\chi^2(2, N = 75) = 0.33$, $p = 0.85$).

3.1. Blast exposure and PTS symptoms: unique associations

EOD operators reporting being within 50 m of a blast during their military career ($n = 50$) endorsed greater PTS symptoms (10.7 ± 1.6) compared with those who did not ($n = 26$, 2.9 ± 1.0) ($F(1,75) = 12.7$, $p = 0.001$, $\eta_p^2 = 0.15$, $1-\beta = 0.94$, $R^2_{adj} = 13.5$). Similarly, those reporting involvement in a vehicle crash or blast ($n = 24$) acknowledged greater PTS symptoms (16.1 ± 2.7) compared with those who did not ($n = 51$, 4.4 ± 0.83) ($F(1,74) = 17.3$, $p < 0.001$, $\eta_p^2 = 0.19$, $1-\beta = 0.98$, $R^2_{adj} = 0.18$). All models were robust to confounding influences of age and TBI diagnosis.

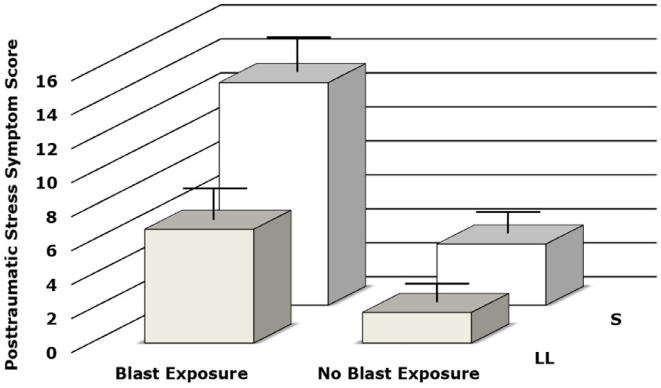

Fig. 1. Blast exposure (50 m) interacts with 5HTTLPR (biallelic) to predict PTS symptoms in EOD operators.

3.2. 5HTTLPR and PTS symptoms: unique associations

S carriers of 5HTTLPR (biallelic version; $n = 47$) registered greater PTS symptoms (9.9 ± 1.6) than homozygous L carriers ($n = 29$, 5.0 ± 1.7) ($F(1,75) = 9.8$, $p < 0.01$, $\eta_p^2 = 0.12$, $1-\beta = 0.87$, $R^2_{adj} = 10.5$). Substituting the triallelic version of 5HTTLPR in this model produced a nearly identical result ($p < 0.05$). All models were robust to the confounding influence of TBI diagnosis.

3.3. Combined associations of blast exposure and 5HTTLPR with PTS symptoms

S carriers of 5HTTLPR (biallelic version) who were within 50 m of a blast (S/blast, $n = 31$) registered decisively higher PTS scores (13.1 ± 2.0) than S/no blast ($n = 16$, 3.6 ± 1.6), LL/blast ($n = 19$, 6.7 ± 2.4), and LL/no blast ($n = 10$, 1.8 ± 1.0) (overall model: ($F(3,75) = 9.4$, $p < 0.001$, $\eta_p^2 = 0.28$, $1-\beta = 0.99$, $R^2_{adj} = 0.25$; Fig. 1). Bonferroni-adjusted post-hoc comparisons confirmed that S/blast differed from all other groups (all $p < 0.017$). Substituting the triallelic version of 5HTTLPR in this model produced a nearly identical result ($p < 0.05$). S carriers of 5HTTLPR (biallelic version) who were involved in a vehicle crash or blast (S/blast, $n = 14$) registered decisively higher PTS scores (20.5 ± 3.1) than S/no blast ($n = 33$, 5.4 ± 1.2), LL/blast ($n = 10$, 10.0 ± 4.3), and LL/no blast ($n = 18$, 2.4 ± 0.9) (overall model: ($F(3,74) = 12.7$, $p < 0.001$, $\eta_p^2 = 0.35$, $1-\beta = 1.00$, $R^2_{adj} = 0.32$). Bonferroni-adjusted post-hoc comparisons confirmed that S/blast differed from every other group (all $p < 0.017$). Substituting the triallelic version of 5HTTLPR in this model produced a nearly identical result ($p < 0.001$). All models were robust to the confounding influences of age and TBI diagnosis.

4. Discussion

The first of its kind, this study demonstrates that blast exposure interacts with 5HTTLPR to predict PTS symptoms in military explosives personnel. Combined models accounted for 25–33% of variance in PTS symptoms.

As hypothesized, blast exposure interacted with 5HTTLPR to predict PTS symptoms. This may offer insight into why some individuals clinically improve after blast exposure, while others do not. Further, the decomposed models, group/marginal means, and plotted PTS symptoms of each group triangulate to imply that the interaction of blast exposure and 5HTTLPR is *multiplicative*. To illustrate, the group and marginal means from the 50 m blast-biallelic 5HTTLPR model showed that (1) mean PTS scores of blast-exposed individuals are approximately 3.5 times that of their non-exposed counterparts, (2) PTS scores of S carriers are roughly twice that of LL carriers, and, ultimately, (3) mean PTS symptoms of blast-exposed S carriers are roughly 7 (3.5 × 2)

times that of unexposed LL carriers. These findings assimilate with an accruing literature showing that 5HTTLPR modulates the impact of diverse stressful life events on behavioral health and resilience (Zhao et al., 2017, Way and Taylor, 2010).

The relationships between blast exposure, 5HTTLPR, and PTS symptoms persisted after controlling for TBI. In practical terms, this implies that blast exposure and genetic predisposition combine to influence PTS symptoms, independent of a clinically diagnosed injury.

An obvious limitation of this study is the basic nature of the self-reported blast exposure constructs in this study. Also, this study assessed PTS symptoms, which should not be construed as an indicator of PTSD.

Declaration of Competing Interest

None.

Acknowledgments

This work was supported by the Congressionally Directed Medical Programs, Joint Program Committee 5, under work unit no. N1909.

References

Armenta, R.F., Rush, T., LeardMann, C.A., Millegan, J., Cooper, A., Hoge, C.W., 2018. Factors associated with persistent posttraumatic stress disorder among U.S. military service members and veterans. BMC Psychiatry 18 (1), 48. https://doi.org/10.1166/s12888-018-1590-5.

Caspi, A., Hariri, A.R., Holmes, A., Uher, R., Moffitt, T.E., 2010. Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. Am. J. Psychiatry 167 (5), 509–527.

Churchman, C., 1967. Guest editorial: wicked problems. Manage. Sci. 14 (4), B141–B142.

Cole, W.R., Bailie, J.M., 2016. Neurocognitive and psychiatric symptoms following mild traumatic brain injury. In: Laskowitz, D., Grant, G. (Eds.), Translational Research in Traumatic Brain Injury. CRC Press/Taylor & Francis Group, Boca Raton, FL, pp. 379–388.

DePalma, R.G., Hoffman, S.W., 2018. Combat blast related traumatic brain injury (TBI): decade of recognition; promise of progress. Behav. Brain Res. 340, 102–105. https://doi.org/10.1016/j.bbr.2016.08.036.

Deputy Secretary of Defense, 2010. Policy guidance for management of concussion/mild traumatic brain injury in the deployed setting (directive-type memorandum 09-033). http://www.dtic.mil/whs/directives/corres/pdf/DTM-09-033.pdf.

Elder, G.A., Dorr, N.P., De Gasperi, R., Gama Sosa, M.A., Shaughness, M.C., Maudlin-Jeronimo, E., Hall, A.A., McCarron, R.M., Ahlers, S.T., 2012. Blast exposure induces post-traumatic stress disorder-related traits in a rat model of mild traumatic brain injury. J. Neurotrauma 29 (16), 2564–2575. https://doi.org/10.1089/neu.2012.2510.

Leech, N.L., Barrett, K.C., Morgan, G.A., 2005. SPSS for Intermediate Statistics: Use and Interpretation, 2nd ed. Lawrence Erlbaum Associates, Mahwah, NJ.

Lewis, C.M., Knight, J., 2012. Introduction to genetic association studies. Cold Spring Harb. Protoc. 2012 (3), 297–306. https://doi.org/10.1101/pdb.top068163.

MacKinnon, D.P., Krull, J.L., Lockwood, C.M., 2000. Equivalence of the mediation, confounding and suppression effect. Prev. Sci. 1 (4), 173–181. https://doi.org/10.1023/A:1026595011371.

Richardson, J.T.E., 2011. Eta squared and partial eta squared as measures of effect size in educational research. Educ. Res. Rev. 6 (2), 135–147. https://doi.org/10.1016/j.edurev.2010.12.001.

Taylor, M.K., Beckerley, S.E., Henniger, N.E., Hernández, L.M., Larson, G.E., Granger, D.A., 2017. A genetic risk factor for major depression and suicidal ideation is mitigated by physical activity. Psychiatry Res. 249, 304–306.

Taylor, M.K., Kviatkovsky, S.A., Hernández, L.M., Sargent, P., Segal, S., Granger, D.A., 2016. Anabolic hormone profiles in elite military men. Steroids 110, 41–48. https://doi.org/10.1016/j.steroids.2016.04.001.

Tschiffely, A.E., Ahlers, S.T., Norris, J.N., 2015. Examining the relationship between blast-induced mild traumatic brain injury and posttraumatic stress-related traits. J. Neurosci. Res. 93 (12), 1769–1777. https://doi.org/10.1002/jnr.23641.

Wald, I., Degnan, K.A., Gorodetsky, E., Charney, D.S., Fox, N.A., Fruchter, E., Goldman, D., Lubin, G., Pine, D.S., Bar-Haim, Y., 2013. Attention to threats and combat-related posttraumatic stress symptoms: prospective associations and moderation by the serotonin transporter gene. JAMA Psychiatry 70 (4), 401–408. https://doi.org/10.1001/2013.jamapsychiatry.188.

Walter, K.H., Levine, J.A., Highfill-McRoy, R.M., Navarro, M., Thomsen, C.J., 2018. Prevalence of posttraumatic stress disorder and psychological comorbidities among U.S. active duty service members, 2006-2013. J. Trauma. Stress 31 (6), 837–844. https://doi.org/10.1002/jts.22337.

Way, B.M., Taylor, S.E., 2010. The serotonin transporter promoter polymorphism is associated with cortisol response to psychosocial stress. Biol. Psychiatry 67 (5), 487–492.

Weathers, F.W., Litz, B.T., Keane, T.M., Palmieri, P.A., Marx, B.P., Schnurr, P.P., 2013. The PTSD Checklist for DSM-5 (PCL-5). Scale available from the National Center for PTSD at. www.ptsd.va.gov.

Xue, C., Ge, Y., Tang, B., Liu, Y., Kang, P., Wang, M., Zhang, L., 2015. A meta-analysis of risk factors for combat-related PTSD among military personnel and veterans. PLoS ONE 10 (3), e0120270. https://doi.org/10.1371/journal.pone.0120270.

Zhao, M., Yang, J., Wang, W., Ma, J., Zhang, J., Zhao, X., Qiu, X., Yang, X., Qiao, Z., Song, X., Wang, L., Jiang, S., Zhao, E., Yang, Y., 2017. Meta-analysis of the interaction between serotonin transporter promoter variant, stress, and posttraumatic stress disorder. Sci. Rep. 7 (1), 16532. https://doi.org/10.1038/s41598-017-15168-0.